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Does early ART in sub-Saharan Africa decrease mortality?

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In 2003, WHO published their first HIV treatment guidelines recommending initiation of antiretroviral therapy (ART) for patients with CD4 counts of 200 cells per μL or less. Because few affordable options existed in sub-Saharan Africa at the time, this recommendation seemed ambitious. An indication that worldwide HIV control efforts have improved in the interim is that the question has shifted from whether anyone can start therapy in the region to whether everyone should. The current focus for WHO and treatment programme planners is whether the threshold of a CD4 count lower than 500 cells per μL should be replaced with a plan to abolish thresholds altogether.

Active debate continues as to whether offering treatment to all people living with HIV worldwide is appropriate and feasible.^{1, 2} Although results from the HIV Prevention Trials Network 052 study³ clearly proved the efficacy of ART for prevention of transmission, little is known about whether early ART decreases mortality in those infected in sub-Saharan Africa. Although three large cohort studies^{4–6} have addressed the question of early ART and mortality, only one of them, the NA-ACCORD trial, showed a survival benefit. None of the three studies included data from patients in sub-Saharan Africa, restricting their generalisability.

In *The Lancet HIV*, Nsanzimana and colleagues⁷ help to address this gap in the scientific literature by analysing data from a national clinical data repository of more than 70 000 patients in Rwanda. Researchers identified a survival benefit for those who linked to care with a CD4 count of more than 500 cells per μL compared with those in lower strata. However, earlier ART initiation without any other indication was not associated with a significant mortality benefit. The authors' use of data wholly within sub-Saharan Africa adds to the study's generalisability and their large sample size adds to the study's validity. What should we make of these conflicting results? As with all retrospective reviews of programmatic data, elements of this analysis should be met with some level of caution. For example, censoring of losses from care could introduce bias if those lost from care at lower CD4 cell counts were more likely to die. Without a randomised clinical trial, estimation of the efficacy of early ART in sub-Saharan Africa will be challenging.

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Fortunately, data are beginning to emerge to examine this question. For example, the completed TEMPRANO study⁸ randomly assigned participants in the Ivory Coast to immediate ART or WHO-based guidelines for ART initiation and reported a reduction in the hazard of death, AIDS, or a serious clinical condition of 40%, which persisted in a subanalysis restricted to those starting with a CD4 count of more than 500 cells per μL . Similarly, the START study,⁹ which randomly assigned individuals with HIV to ART at CD4 counts of more than 500 cells per μL versus less than 350 cells per μL was halted by the data monitoring board because of an approximate halving of clinical events in the early ART group. Whether the benefits in this study were also seen in the four countries (of 36) that enrolled patients in sub-Saharan Africa remains to be seen.

Closer examination of the TEMPRANO and START trials will help to discern optimum efficacy for early ART in sub-Saharan Africa. Cost-effectiveness studies will augment these findings by advising programme planners on a range of costs per life saved. Because roughly 15–20% of patients present to care with a CD4 count of 500 cells per μL in sub-Saharan Africa,^{10, 11} decisions to expand treatment eligibility further will have to be weighed locally and in view of stable or decreasing donor support.¹² For example, provision of therapy for all people living with HIV in Rwanda, where prevalence is less than 5%, will likely have profoundly different ramifications from nations such as Swaziland or South Africa, where the HIV prevalence remains more than 20%.

Ultimately, this study adds important additional data to the continuing discussion about the need to engage people in care early after diagnosis. But whether starting ART at higher CD4 cell counts saves lives when delivered to an entire population of people living with HIV with counts of more than 500 cells per μL is a question that remains unanswered, especially in nations where treatment for all might remain challenging for some time to come.

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